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Familial Risks of Psychotic Disorders and Schizophrenia among Siblings Based on Hospitalizations in Sweden

Xinjun Li^{a,*}, Jan Sundquist^a, Kari Hemminki^{a,b}, and Kristina Sundquist^a

^a Center for Family and Community Medicine, Karolinska Institute, Sweden

^b Division of Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany

Abstract

Objective—Familial risks of psychotic disorders and schizophrenia have been assessed in previous studies. However, the degree of familial clustering in large population datasets remains to be established.

Methods—We conducted a study on familial risks of psychotic disorders and schizophrenia by linking the Multigeneration Register to the nationwide Swedish Hospital Discharge Register. All patients younger than 72 years hospitalized for psychotic disorders or schizophrenia between 1987 and 2004 were included. Standardized incidence ratios (SIRs) were calculated for individuals with affected singleton siblings, twins or spouses compared with individuals whose siblings or spouses had no hospitalization for psychotic disorders or schizophrenia.

Results—A total of 40,228 hospitalized cases were identified of which 3006 were affected sibling pairs. The overall significant familial SIRs were 4.82 for psychotic disorders and 7.34 for schizophrenia. The highest SIRs were found in the younger ages. There were no significant gender differences. The significant SIR for psychotic disorders among twin pairs was 6.40 and the significant SIRs for psychotic disorders among spouses varied between 3.17 and 3.29. Age difference between siblings had no effect on the magnitude of the SIRs.

Conclusions—The findings of the present large-scale study suggest that heritable factors have a stronger effect on psychotic disorders and schizophrenia than environmental factors. Future studies could coordinate epidemiological studies of large populations with molecular biology resources.

Keywords

Sibling risk; schizophrenia; heritability; familial aggregation; population-based

1. INTRODUCTION

Psychotic disorders, including schizophrenia, are characterized by hallucinations and/or delusions as the most predominant symptoms. Schizophrenia is characterized by heterogeneous

*Correspondence to: Dr. Xinjun Li, Center for Family and Community Medicine, Karolinska Institute, Alfred Nobels allé 12, SE-141 83 Huddinge, Sweden, Phone: +46 8 524 887 33, Fax: +46 8 524 887 06, E-mail: xinjun.li@ki.se.

DECLARATION OF INTEREST

There are no conflicts of interest.

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symptoms categorized as positive symptoms (e.g., delusions and hallucinations) or negative symptoms (e.g., flattened affect and social withdrawal). It also includes cognitive deficits. Although the exact etiology of the disorder is not understood, family, twin and adoption studies suggest that genetic causes play an important role in the development of schizophrenia (Laursen et al. 2005). For example, a Danish cohort study found a 3.22-fold increased risk of schizophrenia in first-degree relatives (Laursen et al. 2005). Twin studies have shown that the heritability of schizophrenia is over 80% (Cannon et al. 1998; Cardno et al. 1999).

The inheritance patterns of psychotic disorders including schizophrenia are probably complex. Environmental factors are also important in the development of psychotic disorders. For example, cannabis use, childhood trauma and urbanicity are associated with an increased risk of psychotic disorders (Cougnard et al. 2007; Lataster et al. 2006; Spauwen et al. 2004; Spauwen et al. 2006). Other environmental factors associated with schizophrenia are prenatal exposure to viral infections (Takei et al. 1995) and poor nutrition (Brown et al. 1995).

Previous research suggest that early-onset psychotic disorders may be more strongly genetically influenced than adult-onset psychotic disorders (Pulver et al. 1990; Waddington and Youssef 1996) although these findings have not been consistently reported (Maier et al. 1993; Sham et al. 1994).

For the future success of gene identification efforts, it is important that the familial risks are characterized and that the genetic and environmental components are delineated. The novel contribution of this study is partly its approach; it was based on a nationwide register of all hospitalizations in Sweden between 1987 and 2004, which yielded 21,199 male and 19,029 female cases of psychotic disorders (including schizophrenia). The use of hospitalized cases eliminated potential self-report and recall bias. The data included 3.5 million registered families, which allowed us to analyze familial risks of psychotic disorders for siblings, including twins, and spouses. Schizophrenia was analyzed separately. The Swedish family dataset, i.e., the Multigeneration Register is a validated source that has been proved to be reliable in the study of many familial diseases (Hemminki et al. 2006a; Hemminki et al. 2006b; Sundquist et al. 2006).

2. MATERIAL AND METHODS

2.1 MigMed Research Database

Data used in this study were retrieved from the MigMed database, located at the Center for Family and Community Medicine at the Karolinska Institute in Stockholm. MigMed is a single, comprehensive database constructed from several national Swedish data registers, including but not limited to the Total Population Register, the Multigeneration Register, and the Swedish Hospital Discharge Register (1987–2004) (Rosen and Hakulinen 2005; Statistics Sweden 2005; The National Board of Health and Welfare). The Multigeneration Register includes persons (second generation) born in Sweden in 1932 and later that are linked to their parents (first generation). Families were defined by linking all children to their parents. Sibship can only be defined for the second generation, which was the present study population. Linkages were made to National Census Data in order to determine individual occupational status. The final link was established by adding individual data from the Swedish Hospital Discharge Register, which records complete data on all discharges with dates of hospitalization and diagnoses since 1987. All linkages were performed by using the individual national identification number assigned to each person in Sweden for their lifetime. This number was replaced by a serial number for each individual in order to provide anonymity. The serial number was used to check that each individual was only entered once, for his or her first registered diagnosis of psychotic disorder or schizophrenia. Over 7 million individuals in the second generation were included in this database.

2.2 Outcome variable

Hospitalization for psychotic disorders was retrieved from hospital discharge records reported according to the 9th (1987–1996) and 10th (1997–2004) versions of the International Classification of Diseases. The following ICD codes were included for psychotic disorders: 295, 297, and 298 (ICD-9) and F20 to F29 (ICD-10). The subgroup schizophrenia was analyzed separately (ICD-9: 295 and ICD-10: F20 and F21).

2.3 Individual variables

Gender was categorized into men and women.

Siblings included those who had common parents.

Spouses were defined for the population over 25 years of age through common children.

Age at diagnosis was categorized in 5-year groups and the groups were merged as necessary.

Occupational status was used as an indicator of socioeconomic status divided into six groups according to occupation: (1) Farmers; (2) Unskilled/Skilled workers; (3) White-collar workers; (4) Professionals; (5) Self-employed; and (6) All others.

Geographic region was divided into large cities (cities with a population of more than 200,000, i.e., Stockholm, Gothenburg, and Malmö), Southern Sweden, and Northern Sweden. Geographic region was included as an individual variable in order to adjust for possible differences between geographic regions in Sweden with regard to hospital admissions.

Time period was included in order to adjust for possible differences in hospitalization rates over time.

2.4 Statistical analysis

Person-years were calculated from the start of follow-up on January 1, 1987, to the diagnosis of psychotic disorder or schizophrenia, death, emigration, or the end of the study on December 31, 2004. Age-standardized incidence ratios were calculated for the whole follow-up period, divided into six 3-year periods (1987–1989–1990–1992–1993–1995–1996–1998–1999–2001, and 2002–2004). Standardized incidence ratios (SIRs) were calculated as the ratio of the observed and the expected number of cases (Rothman and Greenland 1998). The expected number of cases was calculated for age (in 5-year groups), gender, period (in 3-year groups), occupational status (in six groups), and region (in three groups). The expected number of cases was based on the number of cases among males and females whose siblings were not affected by psychotic disorders or schizophrenia, i.e. the reference group. Sibling risks were calculated for singleton males and females, or separately for twins, with siblings affected with psychotic disorders or schizophrenia, compared with males and females whose siblings were not affected by these conditions, using the cohort methods as described (Hemminki et al. 2001). Confidence intervals (95% CI) were calculated assuming a Poisson distribution, and they were adjusted for dependence between the sibling pairs (Hemminki et al. 2001).

2.5 Ethical considerations

This study was approved by the Ethics Committee of the Karolinska Institute, Stockholm, Sweden.

3. RESULTS

The MigMed database covered the years 1987 to 2004 in the Swedish Hospital Discharge Register and included 21,199 hospitalized cases of psychotic disorders in males and 19,029 hospitalized cases of psychotic disorders in females between the ages 0 and 72 years (Table 1). Of these, 43.7% and 29.6% represented schizophrenia among the men and women, respectively. In the total number of affected individuals (40,228 hospitalized cases), 7.5% (3006 hospitalized cases) were affected sibling pairs.

A total of 2838 singleton siblings were diagnosed with psychotic disorders, giving an overall familial SIR of 4.82 (95% CI = 3.29–7.08) (Table 2), after adjustment for occupational status, time period, and region. No significant gender differences were observed. A gradient was found for both men and women, so that with increasing age the SIRs decreased but remained significant in all age groups. Table 3 shows that when one sibling was diagnosed with schizophrenia, the overall risk for the other sibling was 7.34 (95% CI = 4.79–11.23). Table 4 shows concordant and discordant significant associations for psychotic disorders and schizophrenia in siblings. There were 84 twin pairs ($N = 168$) diagnosed with psychotic disorders (data not shown), giving an overall SIR of 6.40 (95% CI 3.86–10.52). For schizophrenia, the SIR was 9.64 ($N=66$, 95% CI 5.27–17.35) among twins (data not shown).

Two kinds of analyses were carried out in order to test for the extent of environmental sharing in the observed risks. First, SIRs for siblings according to their age difference were calculated (Table 5). Overall, the age difference had a minor effect on the risks. For example, siblings with an age difference of less than five years had a SIR of 4.67 (95% CI 3.13–6.97) for psychotic disorders and those with an age difference of more than five years had a corresponding SIR of 4.97 (95% CI 3.34–7.39). Second, risks were calculated for spouses hospitalized for psychotic disorders (data not shown). The SIR for the husband was 3.17 (95% CI 2.82–3.55) when the wife was hospitalized for psychotic disorders; for wives the corresponding SIR was 3.29 (95% CI 2.93–3.69).

4. DISCUSSION

The present study provided evidence for strong familial risks of psychotic disorders and schizophrenia in the 0–72-year-old population in Sweden. The overall familial risk for men and women was 4.82, which is in line with earlier publications (Albus and Maier 1995; Cannon et al. 1998; Cardno et al. 1999), including a recent Danish register-based cohort study (Laursen et al. 2005). Traditionally, familial clustering of disease has been studied in the clinical settings where probands and their multiply affected relatives have been identified (Albus and Maier 1995; Maier et al. 1993; Sham et al. 1994). This approach has also been very productive in terms of understanding the genetic factors. The disadvantages include difficulties in obtaining large numbers of cases and in securing unbiased risk estimates. These problems can be overcome in large population registers where data on probands and cases are medically verified and recall bias is eliminated. The novel contribution of the present study is its approach; it was based on a nationwide register of all hospitalized cases in Sweden between 1987 and 2004, which yielded 21,199 male and 19,029 female cases of psychotic disorders including schizophrenia. This study has a number of other strengths. For example, the study population included a well-defined open cohort, i.e. the entire population of Sweden. The unique Swedish Population Registers are almost entirely complete. For example, data on occupational status were nearly 100% complete (99.2%). Additionally, the data in the Swedish Hospital Discharge Register is nearly complete. In 2001, the main diagnosis was missing in only 0.9% of cases and the national registration number in 0.4% of hospitalizations (Rosen and Hakulinen 2005). Because of the national registration number assigned to each individual in Sweden, it was possible to track the records of every individual for the whole follow-up period and follow

each individual in different registers, e.g. the migrant register, which allowed us to calculate exact risk-time. The large number of cases allowed us to analyze age- and gender-specific familial risks. Among both men and women of affected siblings, the risk was higher in younger ages. Previous studies have suggested that the etiology of psychotic disorders and schizophrenia in childhood and adolescence may differ from that of adult-onset, and that early-onset schizophrenia may be more strongly genetically influenced than adult-onset schizophrenia (Pulver et al. 1990; Waddington and Youssef 1996). We found no significant gender differences in familial risks of psychotic disorders and schizophrenia, which is consistent with prior evidence (Cannon et al. 1998; Laursen et al. 2005).

In the present study, the analysis of sibling risks for psychotic disorders and schizophrenia according to their age difference gives no indication of environmental sharing, assuming that a smaller age difference is a proxy for environmental sharing. Moreover, if environmental factors are expected to contribute to the late-onset cases, whereas the heritable causes would contribute to the early-onset cases, the relatively low spouse correlation (compared with the risks among siblings at younger ages) also supports the notion that heritable factors have a stronger effect than environmental factors. However, a caveat is that spouses have a shared environment only in adult ages, which also means that they could have been diagnosed with the disease before they became partners. Finally, twin studies have found no evidence of shared environmental effects on schizophrenia (Cannon et al. 1998; Cardno et al. 1999).

There are some limitations in the present study. Undoubtedly, some sibling pairs were lost because one of the siblings could have been hospitalized before the start of the follow-up. There could also be problems with selection bias. However, affordability of health care is unlikely to be a selective factor in Sweden because of the equal access to primary and hospital care. If siblings in general should have a tendency to seek or receive hospitalization, we would assume that siblings who are close in age would show the highest risk. This, however, was contrary to our findings. Finally, we were unable to test for the validity of the diagnoses because our data were based on the entire population. However, we only used main diagnoses for psychotic disorders and schizophrenia recorded in the hospital registers, which increases the possibility that the diagnoses are valid.

5. CONCLUSION

The higher familial risks in singleton siblings and twins compared to spouses provide strong genetic epidemiological evidence for the overall heritable effects with regard to psychotic disorders and schizophrenia. Progress in the understanding of the heritable basis of psychotic disorders and schizophrenia requires coordinated efforts in genetic epidemiology and molecular genetics.

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Table 1
Number of hospitalized cases of psychotic disorders and schizophrenia in the 0- to 72-year-old population from Sweden

	Men			Women			All					
	All cases		With sibling history	All cases		With sibling history	All cases		With sibling history			
	Cases	%	Cases	%	Cases	%	Cases	%				
Psychotic disorders	21199	100.0	1628	100.0	19029	100.0	1378	100.0	40228	100.0	3006	
Schizophrenia	9256	43.7	824	50.6	5629	29.6	503	36.5	14885	37.0	1327	44.1

Table 2
Familial SIRs for psychotic disorders in siblings by age at diagnosis

Age at diagnosis	Men			Women			All		
	O	SIR	95%CI	O	SIR	95%CI	O	SIR	95%CI
<20	68	12.18	6.69	21.85	6.43	3.15	102	9.39	5.41
20–29	441	6.56	4.22	10.19	5.89	3.69	713	6.29	4.13
30–39	504	4.77	3.09	7.37	4.92	3.16	923	4.84	3.20
40–49	367	4.35	2.77	6.82	3.98	2.52	703	4.17	2.73
50–59	134	3.49	2.07	5.85	4.15	2.54	335	3.86	2.44
>=60	27	3.65	1.70	7.52	3.38	1.66	62	3.49	1.89
All	1541	5.00	3.36	7.43	4.64	3.10	2838	4.82	3.29

O = observed number of cases; SIR = standardized incidence ratio; CI = confidence interval

Bold type: 95% CI does not include 1.00.

Table 3
Familial SIRs for schizophrenia in siblings by age at diagnosis

Age at diagnosis	Men			Women			All					
	O	SIR	95%CI	O	SIR	95%CI	O	SIR	95%CI			
<20	10	26.33	8.87	68.74	2	5.33	0.36	27.73	12	15.90	5.78	39.39
20–29	81	8.29	4.65	14.57	45	9.39	4.84	17.78	126	8.65	5.10	14.57
30–39	137	7.18	4.26	12.01	77	7.42	4.14	13.12	214	7.27	4.47	11.75
40–49	110	7.00	4.07	11.93	76	7.39	4.12	13.09	186	7.15	4.36	11.68
50–59	38	5.84	2.92	11.34	37	6.79	3.38	13.25	75	6.27	3.49	11.12
>=60	5	5.24	1.17	17.43	3	3.19	0.43	13.37	8	4.22	1.28	11.83
All	381	7.27	4.64	11.37	240	7.45	4.62	11.96	621	7.34	4.79	11.23

O = observed number of cases; SIR = standardized incidence ratio; CI = confidence interval

Bold type: 95% CI does not include 1.00.

Table 4
Concordant and discordant (in italics) familial SIRs for psychotic disorders and schizophrenia in siblings

Subtype	Psychotic disorders			Schizophrenia		
	O	SIR	95%CI	O	SIR	95%CI
Psychotic disorders	2838	4.82	3.29	1183	5.53	3.69
Schizophrenia	1253	5.46	3.65	621	7.34	4.79

O = observed number of cases; SIR = standardized incidence ratio; CI = confidence interval
Bold type: 95% CI does not include 1.00.

Table 5
Familial SIRs for psychotic disorders and schizophrenia in siblings by age difference

	<5 years				>=5 years			
	O	SIR	95% CI	O	SIR	95% CI	O	95% CI
Psychotic disorders	1332	4.67	3.13	1506	4.97	3.34	739	7.39
Schizophrenia	582	5.23	3.40	671	5.69	3.72	868	8.68

O = observed number of cases; SIR = standardized incidence ratio; CI = confidence interval
Bold type: 95% CI does not include 1.00.